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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,772	02/25/2002	Peter Droge	DEBE:008US	4391

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,772	DROGE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,30,32-39,43-51 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-30, 32-39, 43-51 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 10/04/06 was entered.

It is noted that Applicants elected previously **without traverse** of Group I, drawn to a method of sequence specific recombination of DNA in a eukaryotic cell, **wherein the method is performed in a cell culture (or *ex vivo*)**, in the Amendment filed on 8/29/03.

Claims 29-30, 32-39, 43-51 and 58 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The rejection under 35 U.S.C. 112, first paragraph, for the lack of Written Description was withdrawn in light of Applicant's amendment.

Claim Objections

Claim 29 and its dependent claims are objected to because they contain a non-elected embodiment (a eukaryotic cell present in a vertebrate organism; Group II). Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 29-30, 32-35, 44-45, 49 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al. (US 5,888,732) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) for the same reasons already set forth in the Office Action mailed on 5/4/06 (pages 5-8). ***The same rejection is restated below for Applicant's convenience.***

Hartley et al disclose a method of making chimeric DNA comprising the steps: (a) combining *in vitro* or *in vivo*, (b) an Insert Donor DNA molecule, comprising a desired DNA segment flanked by a first recombination site and a second recombination site, wherein the first and second recombination sites do not recombine with each other; (c) a Vector Donor DNA molecule containing a third recombination site and a fourth recombination site, wherein the third and fourth recombination site do not recombine with each other; and (d) one or more site specific recombination proteins capable of recombining the first and third recombination sites and/or the second and fourth

recombination sites (see Summary of the Invention, and Figures 1-2A-F). Figure 1 depicts a general method of Hartley et al., involving two recombination events with two different recombinases that recognize different recombination sites. Hartley et al also teach that the exchange of DNA segments can be achieved by the use of various recombination proteins described in the art, including λ Integrase (col. 13, line 57 continues to line 24 of col. 16). Hartley et al further teach examples of recognition sequences to be utilized include attB, attP, attL, and attR sequences which are recognized by the recombinase enzyme λ Integrase (col. 8, lines 43-63). The disclosed attB sequence of SEQ ID NO:32 comprises the sequence that is identical to SEQ ID NO:1 of the present application, and therefore the corresponding attP recombination sequence must have the same SEQ ID NO: 2 of the present application, or at least a derivative thereof. Furthermore, the attL and attR recombination sequences that are catalyzed by λ Integrase taught by Hartley et al. must have the same SEQ ID NO:3 and SEQ ID NO:4, respectively, or at least a derivative thereof. The desired DNA segment includes a selectable marker (DNA segments that encode beta-galactosidase, GFP or cell surface proteins), an antisense oligonucleotide or a toxic gene (col. 9, lines 5-36), and that host cells include *E.coli* cell lines as well as eukaryotic cells (col. 13, lines 35-55). Hartley et al. also teach the use of integrase in the presence of λ protein Xis (excise) to catalyze the reaction of attR and attL to form attP and attB, and in effect reverse the integrative recombination between attP site and attB site mediated by λ Integrase (col. 15, lines 1-4), as well as the use of IHF proteins for the recombination at attB and attP sites (col. 14, lines 26-30). Hartley et al. also teach engineered att

recombination sites having one or multiple mutations to enhance specificity or efficiency of the recombination reaction, and that a tripartite protein fusion could be accomplished with parental plasmids containing recombination sites attR1 and attR2; attL1 and attL3; and attR3 and attL2 (col. 16, lines 26-61; col. 17, line 47 continues to line 46 of col. 18). With respect to claim 30, the method for introducing the Insert Donor and the Vector Donor into a cell is a recombinant method, and such a method would result in the random incorporation of any one of the Insert Donor and the Vector Donor in a DNA of the cell.

Hartley et al do specifically teach the use of any modified λ Integrase, specifically Int-h or Int h/218.

However, at the effective filing date of the present application Christ & Droge already taught the mutant λ Integrases, Int-h and Int-h/218, that are capable of mediating substrate deletion through λ site-specific recombination in prokaryotes in the absence of co-factors Fis and Xis (see at least the abstract; page 829, right hand column, top and bottom of the first full paragraph). Christ & Droge further teach that the potential of these mutants to perform recombination in the absence of accessory factors is due to their enhanced affinity for core sites, and that Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase (page 827, left column, second full paragraph; page 828, left column, top of last paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Hartley et al. by also utilizing the mutant λ Integrases, Int-h and

Int-h/218, of Christ & Droge in either the integrative or the excision recombination step or both for the making a chimeric DNA due to the advantages offered by these mutant Integrases, at least the mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than the wild-type Intergrase. Please also note that this modified method does not exclude the use of wild-type λ Integrase altogether in the method of Hartley et al, depending on whether the mutant Integrases would be employed in both recombination steps.

An ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Christ & Droge, at least these mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hartley et al., Christ & Droge, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on 10/4/06 (pages 6-9) have been fully considered but they are respectfully not found persuasive.

Once again, Applicants argue mainly that Hartley et al use exclusively the **wild-type** lambda integrase in prokaryotic and eukaryotic host cells, while Christ & Droge relates exclusively to integrative and excisive attL/attR and attP/attB recombination performed in **prokaryotes** using modified lambda integrases such as **Int-h and Int-h/218**. Applicants further argue that Christ & Droge does not give the slightest hint that the described modified integrases could also promote recombination events in eukaryotic cells and that it is well known that the organization of the prokaryotic genome is distinct from the eukaryotic genome. Whereas the prokaryotic genome is circular and condensed due to negative supercoiling and architectural proteins like IHF, the eukaryotic genome is comprised of linear DNA molecules which are highly condensed in nucleosomes by histone proteins. Without the aid of topologically underwound DNA, which exists only in prokaryotic cells, it was reasonable to assume that mutant Int proteins can not function. Therefore, there was no reasonable expectation of success that these modified integrases would also work in eukaryotic cells (i.e., having a eukaryotic DNA susbtrate). Applicants also noted that the examiner is incorrect for arguing that eukaryotic recombinantion is not required by most of the instant claims because there is only a single independent claim that clearly recites "A method of sequence specific recombination of DNA in a eukaryotic cell".

Firstly, please note that the claims recite "said cell comprising a first DNA segment". This does not necessarily mean that the DNA segment has to be a eukaryotic DNA or the DNA segment has to be incorporated into the genome of the eukaryotic cell. The DNA segment encompasses a bacterial DNA plasmid segment that

is present in a eukaryotic cell, and that it is not necessarily incorporated into the genome of the eukaryotic cell. The claims as written are broad, and Applicants read the specification into the claims as evidenced by Applicant's arguments presented above.

Secondly, Hartley et al. taught clearly the use of a wild type λ Integrase in both ***E.coli* cell lines** as well as **eukaryotic cells** (col. 13, lines 35-55), and that Christ & Droge clearly taught that in the absence of IHF, **wild-type Int and the two variants namely Int-h and Int-h/218 exclusively catalyze inversion** (page 829, right hand column, top of the first full paragraph). Since wild-type λ Integrases are capable of mediating sequence specific recombination events in both eukaryotic and prokaryotic cells, and it is known that the conditions required by a wild-type λ Integrase to mediate a sequence specific recombination event **in prokaryotic cells are even more stringent than those** required by the Int-h as evidenced by the teachings of Lange-Gustafson et al. (J. Biol. Chem. 259:12724-12732, 1984; see at least the abstract), then why wouldn't these Integrase mutants, particularly Int-h, would not function in eukaryotic cells? Moreover, Lange-Gustafson et al also taught clearly that **Int-h uses supercoiled DNA more effectively than non-supercoiled DNA as a substrate for recombination** (see abstract). Thus, in light of the teachings of Hartley et al., Christ & Droge along with the evidence provided by the teachings of Lange-Gustafson et al., it is reasonable for a skilled artisan to expect that these mutant integrases, Int-h and Int-h/217, to function in eukaryotic cells to mediate sequence specific recombination in both eukaryotic and/or prokaryotic DNA segments.

Thirdly, the examiner also notes that none of the instant claims requires the specific use of these mutant Integrases **to carry out the deletion of any DNA segment in a eukaryotic type without the use of a Xis factor or Xis factor gene**. Furthermore, Hartley et al. also teach the use of integrase in the presence of λ protein Xis (excise) to catalyze the reaction of attR and attL to form attP and attB.

As already noted above, an ordinary skilled artisan would be motivated to modify the method taught by Hartley et al. by utilizing the mutant λ Integrases, Int-h and Int-h/218 of Christ & Droge due to the advantages offered by the mutant integrases, at least that the mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than the wild-type Intergrase.

The Declaration under 37 CFR 1.132 filed 10/4/06 is insufficient to overcome the rejection of claims 29-30, 32-35, 44-45, 49 and 58 based upon Hartley et al. (US 5,888,732) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) applied under 35 U.S.C. 103(a) as set forth in the last Office action because of the breadth of the claims as written and in light of the teachings of Hartley et al., Christ & Droge along with the evidence provided by the teachings of Lange-Gustafson et al. as discussed in the preceding paragraphs.

Claims 36-39 and 49-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hartley et al. (US 5,888,732) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) as applied to claims 29-30, 32-35, 44-45, 49 and 58 above,

and further in view of Crouzet et al. (US Patent 6,143,530) for the same reasons already set forth in the Office Action mailed on 5/4/06 (pages 10-13). ***The same rejection is restated below for Applicant's convenience.***

The combined teachings of Hartley et al and Christ & Droge have been discussed above. However, none of the references specifically teaches the modified method by providing to a eukaryotic cell a third DNA segment comprising an Int gene and a fourth DNA segment comprising Xis factor gene, wherein said third DNA segment and said fourth DNA segment comprises a regulatory sequence effecting a spatial and/or temporal expression of the Int gene or the Xis factor gene, even though Hartley et al teach the use of an Int in the presence of λ protein Xis (excise) to catalyze the reaction of attR and attL Please also note that the above modified method does not exclude the use of wild-type λ Integrase altogether in the method of Hartley et al, depending on whether the mutant Integrases would be employed in both recombination steps. With respect to claims 50-51, none of the references specifically teaches the modified method including the introduction of a DNA sequence comprising a Xis factor gene containing a regulatory sequence effecting a spatial and/or temporal expression of the Xis factor gene.

However, at the effective filing date of the present application Crouzet et al already taught a method for producing DNA molecules by excision from a plasmid or from a chromosome by site-specific recombination, wherein the site-specific recombination is carried out in a host cell (including eukaryotic cells such as yeasts, animal cells, plant cells, mammalian cells such as CHO, COS and mouse NIH3T3; col.

9, lines 48-60) or *in vitro*, and wherein the site-specific recombination is carried out by means of various systems which lead to site-specific recombination between sequences (col. 3, line 27 continues to line 20 of col. 4; Figures 1-2). Specifically, Crouzet et al already disclosed that the gene or genes of interest flanked by the two sequences permitting site-specific recombination, positioned in the direct orientation in a vector, a phage or a virus, and the specific recombination sequences and recombinases used can belong to different structural classes, including the integrase family of bacteriophage λ and the attP and attB sequences catalyzed by the phage lambda integrase (col. 4, lines 21-52; col. 5, lines 32-41). More importantly, Crouzet et al teach that the recombinase used can be under the control of a promoter or a system of inducible promoters, and it can be carried by a plasmid, a phage or even in the non-therapeutic region of the recombinant DNAs (col. 7, line 45 continues to line 39 of col. 8).

It would have been obvious for an ordinary skilled artisan to further modify the method taught by Hartley et al and Christ & Droge by providing the eukaryotic cell a nucleic acid molecule encoding an Integrase and/or a protein Xis, operably linked to a regulatory promoter, instead of using Integrase protein and protein Xis as disclosed in the method of Hartley et al. for making a chimeric DNA *in vitro* and *in vivo*, in light of the teachings of Crouzet et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Crouzet et al already taught at least that the provision of an Integrase in the form of an expression cassette under the control of an inducible

promoter or temperature-sensitive systems allows the induction of site-specific recombination *in vivo* in a regulated manner by simply placing the cells in culture at the desired time under the conditions for the expression of the recombinase gene (at least col. 8, lines 3-17). Similarly, the provision of an Xis factor gene in the form of an expression cassette under the control of an inducible promoter or temperature-sensitive systems would also allow the induction of site-specific excision by Integrase in a regulated manner.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Hartley et al., Christ & Droge, Crouzet al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

It is noted that Applicants did not present any arguments specifically to the above rejection in the Amendment filed on 10/4/06.

Claims 29-30, 32-33, 44-48 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) for the same reasons already set forth in the Office Action mailed on 5/4/06 (pages 13-16). ***The same rejection is restated below for Applicant's convenience.***

Crouzet et al teach a method for producing therapeutic DNA molecules by excision from a plasmid or from a chromosome by site-specific recombination, wherein the site-specific recombination is carried out in a host cell or *in vitro*, and wherein the site-specific recombination is carried out by means of various systems which lead to site-specific recombination between sequences (col. 3, line 27 continues to line 20 of col. 4; Figures 1-2). Specifically, Crouzet et al disclose that the gene or genes of interest flanked by the two sequences permitting site-specific recombination, positioned in the direct orientation in a vector, a phage or a virus, and the specific recombination sequences and recombinases used can belong to different structural classes, including the integrase family of bacteriophage λ and the attP and attB sequences catalyzed by the phage lambda integrase (col. 4, lines 21-52; col. 5, lines 32-41). The disclosed attB sequence is identical to SEQ ID NO:1 of the present application (see SEQ ID NO:6), and therefore the corresponding attP recombination sequence must have the same SEQ ID NO: 2 of the present application, or at least a derivative thereof. Additionally, Crouzet et al. teach that their genetic constructs can be used for the construct of cell hosts having disclosed elements integrated in their genomes (col. 4, lines 4-9, and Figure 1). Crouzet et al further teach that the recombinase used can be under the control of a promoter or a system of inducible promoters, and it can be carried by a plasmid, a phage or even in the non-therapeutic region of the recombinant DNAs (col. 7, line 45 continues to line 39 of col. 8), and that any type of host cell can be used including eukaryotic cells such as yeasts, animal cells, plant cells, mammalian cells such as CHO, COS and mouse NIH3T3 (col. 9, lines 48-60). Crouzet et al also disclose

that their genetic constructs comprise one or more genes of interest such as the genes coding for enzymes, hormones, growth factors, apolipoproteins, tumor suppressor genes, suicide genes, natural or artifical immunoglobulin or an antigenic peptide (col. 13, lines 14-50).

Crouzet et al do not specifically teach the use of any modified λ Integrase, specifically Int-h or Int h/218 in their method of producing therapeutic DNA molecules, even though they teach that any specific recombination sequences and appropriate recombinases can be used, including those belonging to the bacteriophage λ system.

However, at the effective filing date of the present application Christ & Droge already taught the mutant λ Integrases, Int-h and Int-h/218, that are capable of mediating substrate deletion through λ site-specific recombination in prokaryotes in the absence of co-factors Fis and Xis (see at least the abstract; page 829, right hand column, top and bottom of the first full paragraph). Christ & Droge further teach that the potential of these mutants to perform recombination in the absence of accessory factors is due to their enhanced affinity for core sites, and that Int-h is known to recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase (page 827, left column, second full paragraph; page 828, left column, top of last paragraph).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method taught by Crouzet et al by utilizing specifically the mutant λ Integrases, Int-h and Int-h/218, of Christ & Droge in their method of producing therapeutic DNA molecules due to the advantages offered by the mutant integrases, at least the mutant

Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than the wild-type Intergrase.

An ordinary skilled artisan would have been motivated to carry out the above modification because as taught by Christ & Droge, at least these mutant Integrases can recombine pairs of att sites which differ in their overlap sequence by one or more base-pairs more efficiently than wild-type Integrase.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 10/4/06 (page 9) have been fully considered but they are respectfully not found persuasive.

Once again, Applicants argue that Crouzet et al use exclusively the **wild-type** lambda integrase, while Christ & Droge relates exclusively to integrative and excisive attL/attR and attP/attB recombination performed in **prokaryotes**. There was no motivation for combining these two very distinct systems, and even if there were, there was no likelihood of success that they would be compatible, i.e., that the modified integrases of Christ & Droge would function in a eukaryotic system.

Please refer to the same examiner's response to the same Applicant's arguments for the rejections of claims 29-30, 32-35, 44-45, 49 and 58 above.

Claims 29 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crouzet et al. (US Patent 6,143,530) in view of Christ & Droge (J. Mol. Biol. 288:825-836, 1999; IDS) as applied to claims 29-30, 32-33, 44-48 and 58 above, and further in view of Capecchi et al. (US 5,464,764) for the same reasons already set forth in the Office Action mailed on 5/4/06 (pages 16-18). ***The same rejection is restated below for Applicant's convenience.***

The teachings of Crouzet et al. and Christ & Droge have been discussed above. However, neither Crouzet et al nor Christ & Droge teach that the first and/or the second DNA segment further comprising a sequence effecting integration of said first and/or second DNA segment into the genome of a cell by homologous recombination, even though Crouzet et al teach specifically that the genetic constructs can be used for the construct of cell hosts having disclosed elements integrated in their genomes (col. 4, lines 4-9, and Figure 1).

However, at the effective filing date of the present application Capecchi et al. already describe a well-known method and a positive-negative selector vectors comprising sequences to be introduced in the genome of a target cell by the homologous recombination approach (see abstract and Figure 1).

It would have been obvious for an ordinary skilled artisan to further modify the modified method of Crouzet et al and Christ & Droge by introducing the genetic

construct in the form of a positive-negative selector vector described by Capecchi et al. into a target host cell capable of homologous recombination to incorporate their genetic construct in the genome of the host cell as specifically taught by Crouzet et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the approach taught by Capecchi et al. overcomes many problems associated with random integration, and that the gene of interest can be introduced into any predetermined region of the genome of a target host cell.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge and Capecchi et al, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments with respect the above rejection in the Amendment filed on 10/4/06 (pages 9-10) have been fully considered but they are respectfully not found persuasive.

Once again, Applicants argue mainly that Capecchi et al. fails to address the issue whether modified integrases would work in eukaryotic cells to supplement the defects of Crouzet et al. and Christ & Droge. Additionally, there was no motivation for combining the primary and secondary references and there was no likelihood of success that they would work together.

With respect to the defects of Crouzet et al and Christ & Droge, please refer to the same examiner's response to the same Applicant's arguments for the rejections of claims 29-30, 32-35, 44-45, 49 and 58 above.

With respect to the lack of motivation and no likelihood of success, as noted in the above rejection an ordinary skilled artisan would have been motivated to carry out the above modification because the approach taught by Capecchi et al. overcomes many problems associated with random integration, and that the gene of interest can be introduced into any predetermined region of the genome of a target host cell. An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Crouzet et al., Christ & Droge and Capecchi et al, coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Primary

QUANG NGUYEN, PH.D
PATENT EXAMINER